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(54) Title: METAL IMPLANTS

(57) Abstract: A metal implant for use in a surgical procedure is provided with a surface layer that is integral with the metal substrate, and which incorporates a biocidal material. The surface layer may be grown from the metal substrate, by anodising, and the biocidal material incorporated in it by ion exchange. Alternatively the layer may be deposited by electroplating, followed by diffusion bonding so as to become integral with the metal substrate. In either case, silver is a suitable biocidal material; and both the release rate and the quantity of biocidal material should be low to avoid toxic effects on body cells. Electropolishing the surface before formation of the surface layer is also beneficial, and this may be achieved by electropolishing.

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### Metal Implants

This invention relates to metal implants for use in surgical procedures, and in particular to the  
5 introduction of a biocidal material into such implants to suppress or control infection.

Various surgical procedures require the use of implants. For example cancerous bone may be removed, in  
10 prosthetic surgery, to be replaced by a metal implant. Such an implant may for example be of titanium alloy, which is very strong and relatively light. To ensure a hard-wearing surface the provision of a titanium nitride coating has been suggested. There is furthermore a risk  
15 of introducing infection when implanting such metal implants, and it has been suggested that metallic silver might be electroplated onto metal implants, the silver being a biocidal material that can control infection without causing toxic effects to the patient. However  
20 such coatings, whether of titanium nitride or silver, may be undercut due to corrosion from body fluids, so that the coating may detach from the implant, which may can increase wear and cause tissue damage.

25 According to the present invention there is provided an implant for use in a surgical procedure, the implant comprising a metal substrate and a surface layer that is integral with the metal substrate, the layer  
30 incorporating a biocidal metal deposited from a solution.

The invention also provides a method of producing such an implant.

Such an integral surface layer may be generated by  
35 growing the layer from the metal itself, for example by an anodising process; or alternatively by depositing the

layer for example by electroplating, followed by diffusion bonding so that the layer becomes integral with the metal of the implant. Anodising forms an adherent oxide layer, although if it is carried out in phosphoric acid then a phosphate may be formed. Such an adherent phosphate layer may also be modified to form a hydroxyapatite layer, which can stimulate bone growth.

The biocidal material should preferably be effective for at least 6 weeks, preferably for up to 6 months after surgery, and the release rate should be low to avoid toxic effects on body cells. Furthermore the total quantity of biocidal material is preferably also limited to minimize any toxic effects.

15

It is also desirable if the surface is highly polished before production of the surface layer. This may for example be achieved by electropolishing.

In principle, a range of different metals may be used for the biocidal metal. In particular, if the layer is a metal layer deposited by electroplating then it clearly must be stable to corrosion. Gold, platinum, iridium and palladium would be potentially suitable, although expensive; silver is preferable as it is not particularly soluble in body fluids due to the presence of chloride ions and the low solubility of silver chloride. If the surface layer contains the biocidal metal in ionic form, then a wider range of metals would be possible. In addition to the elements already mentioned, copper, tin, antimony, lead, bismuth and zinc might be used as ions combined into an insoluble matrix for example of metal oxide or metal phosphate. The rate of release would be controlled, in this case, primarily by the strength of the absorption of the metal ions in the matrix.

The metals that may be used to make such prosthetic implants are typically a form of stainless steel, a titanium alloy, or a cobalt/chromium alloy, although zirconium could also be used. The standard alloys for this purpose are titanium 90% with 6% aluminium and 4% vanadium (British standard 7252), or chromium 26.5-30%, molybdenum 4.5-7%, and the remainder cobalt (British standard 7252 part 4).

10        Preferably the implant is initially polished to provide a very smooth surface. Both stainless steel (chromium/iron/nickel) and cobalt/chromium alloy can be electro-polished using as electrolyte a mixture of phosphoric acid and glycerine, or a mixture of phosphoric  
15 acid and sulphuric acid. Titanium alloy can be electro-polished using acetic acid, or a mixture of nitric and hydrofluoric acids. Alternatively the implants might be subjected to a combination of anodic passivation with mechanical polishing, which may be referred to as  
20 electrolinishing, this process removing the oxide that protects surface roughness, the surface at that point then being electrochemically re-passivated, so producing a mirror-smooth finish. Various electrolytes are  
25 suitable for this purpose, including nitric acid mixed with sulphuric acid, sodium hydroxide, sodium phosphate, or sodium hydroxide mixed with sodium nitrate.

After polishing the surface of the metal, either silver deposition or surface conversion can take place.  
30 Considering surface conversion first, a layer of metal oxide or phosphate may be formed by anodising in a suitable electrolyte, so that the oxide or phosphate layer builds out from the surface of the metal. Biocidal metal ions can then be absorbed from an aqueous salt  
35 solution into the oxide or phosphate matrix, for example the ions  $\text{Ag}^+$  or  $\text{Cu}^{++}$ . Cations of palladium, platinum or

even ruthenium could be absorbed in a similar way. If desired, deposited silver, platinum or palladium ions could then be converted to metal, or deposited ruthenium ions converted to insoluble  $\text{RuO}_2$ , within the oxide or phosphate surface coating, this reaction being performed chemically or electrochemically or by light.

Considering now silver deposition, the coating should be thin to prevent toxic effects. A high degree of adherence to the underlying metal can be ensured by first removing the surface oxide layer by anodic etching, followed by a brief reversal of polarity in the presence of appropriate ions, so as to cover the surface with a thin coating of silver. This may be repeated to ensure there are no pin-holes. The plating electrolyte may include hydrofluoric acid, or may be an alkaline cyanide electroplating electrolyte. After deposition, the silver coating should be diffusion bonded so as to form an inter-metallic layer, by heating the implant to an elevated temperature. Typically it should be heated to above  $800^\circ\text{C}$ , preferably between  $810^\circ\text{C}$  and  $950^\circ\text{C}$ , in an inert atmosphere for example of argon for a period of between 1 and 6 hours. This substantially eliminates the risk of coating delamination. However with titanium-based implants the temperature must not exceed  $850^\circ\text{C}$  as titanium would undergo a phase change from alpha to beta form above this temperature.

In place of silver, other metals such as platinum or palladium may be electro-deposited and then thermally treated in a similar fashion so as to form an inter-metallic layer.

The invention will now be further and more particularly described, by way of example only.

A hip implant is made of titanium alloy (Ti/Al/V). The implant is cleaned ultrasonically using first acetone as the liquid phase, and then a 1 M aqueous solution of sodium hydroxide, and is then rinsed in de-ionised water.

5 The cleaned implant is then immersed in a stirred 12 weight % solution of phosphoric acid, and is anodised for 2 hours at a maximum voltage of 10 V and a maximum current of 10 mA/cm<sup>2</sup>, so as to form a surface coating of titanium phosphate. It is then rinsed in de-ionised

10 water again. The surface, which is initially pale grey, turns to a darker matt grey as a consequence of the anodising, with a slightly yellow hue.

The implant is then immersed in a stirred 0.1 M

15 aqueous solution of silver nitrate, and left for 2 hours.

As a result of ion exchange there is consequently some silver phosphate in the titanium phosphate coating. The implant is then ready to be implanted. During exposure to body fluids there will be a slow leaching of silver

20 ions from the phosphate layer, so that any bacteria in the immediate vicinity of the implant are killed. Infection arising from the implant is therefore suppressed.

25 Experimental samples of this titanium alloy were cleaned, anodised to form a layer of titanium phosphate, and then subjected to ion exchange to form silver phosphate, following the procedure described above. One sample was placed in direct daylight for 110 hours; the

30 exposed surface became darkened as a result of this exposure to daylight, indicating the formation of silver metal by photo-reduction. The other sample was immersed in a solvent containing a mixture of 4 M nitric acid and 0.5 M sodium fluoride (equivalent to hydrofluoric acid)

35 to dissolve the coating. The dark grey surface coating was removed completely within 3 minutes, leaving a

silver-grey finish. The resulting solution was analyzed for the presence of silver by atomic absorption spectrometry, and the concentration of silver was found to be equivalent to an average surface loading of 735  $\mu\text{g}/\text{cm}^2$ .

Claims

1. An implant for use in a surgical procedure, the  
implant comprising a metal substrate and a surface layer  
5 that is integral with the metal substrate, the layer  
incorporating a biocidal metal deposited from a solution.
2. An implant as claimed in claim 1 wherein the  
integral surface layer is generated by growing the layer  
10 from the metal.
3. An implant as claimed in claim 2 wherein the surface  
layer is generated by an anodising process.
- 15 4. An implant as claimed in claim 3 wherein the surface  
layer comprises a metal phosphate.
5. An implant as claimed in any one of claims 2 to 4  
wherein the biocidal metal comprises metal ions absorbed  
20 within the surface layer.
6. An implant as claimed in claim 5 wherein the  
biocidal material comprises silver.
- 25 7. An implant as claimed in claim 1 wherein the  
integral surface layer is generated by first depositing  
the layer and then subjecting the layer and the substrate  
to diffusion bonding so that the layer becomes integral  
with the metal of the substrate.  
30
8. An implant as claimed in any one of the preceding  
claims wherein the surface of the implant is highly  
polished before provision of the surface layer.



9. A method of making an implant for use in a surgical procedure, the implant comprising a metal substrate, and the method comprising forming a surface layer on the substrate which is integral with the metal substrate, and  
5 incorporating a biocidal metal in the layer by deposition from a solution.
10. A method as claimed in claim 9 comprising anodising the surface of the substrate to form the integral surface  
10 layer.
11. A method as claimed in claim 10 wherein silver ions are incorporated in the surface layer by contact with a solution containing silver ions.  
15
12. A method as claimed in claim 9 wherein the surface layer is a metal layer deposited by electroplating, and is subsequently rendered integral with the substrate by a heat treatment to cause diffusion bonding.  
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## INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 7 A61L27/30 A61F2/30

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 113 636 A (OGLE MATTHEW F) 5 September 2000 (2000-09-05) column 4, line 15 - line 21 column 6, line 43 - line 62 column 7, line 1 - line 29 column 8, line 18 - line 35 column 8, line 57 - line 67 ---	1,2,4-6, 9,11
X	WO 99 01089 A (UNIV BROWN RES FOUND ;VALENTINI ROBERT F (US)) 14 January 1999 (1999-01-14) page 6, line 2 - line 5 page 8, line 6 -page 10, line 22 page 17, line 6 - line 29 page 19, line 1 - line 13 --- -/--	1,2,4,5, 7,9,12

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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